

# Historical Perspective on Lead Biokinetic Models

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A historical review of the development of biokinetic model of lead is presented. Biokinetics is interpreted narrowly to mean only physiologic processes happening within the body. Proceeding chronologically, for each epoch, the measurements of lead in the body are presented along with mathematical models in an attempt to trace the convergence of observations from two disparate fields—occupational medicine and radiologic health—into some unified models. Kehoe's early balance studies and the use of radioactive lead tracers are presented. The 1960s saw the joint application of radioactive lead techniques and simple compartmental kinetic models used to establish the exchange rates and residence times of lead in body pools. The applications of stable isotopes to questions of the magnitudes of respired and ingested inputs required the development of a simple three-pool model. During the 1980s more elaborate models were developed. One of their key goals was the establishment of the dose-response relationship between exposure to lead and biologic precursors of adverse health effects. — *Environ Health Perspect* 106(Suppl 6):1461–1465 (1998). <http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-6/1461-1465rabinowitz/abstract.html>

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Consideration of lead biokinetics from a historical perspective promises to provide some useful insights. The evolution of our thinking on this topic reveals which concerns or problems are transient, dealt with once years ago and no longer requiring further validation, and which issues seem to be recurring, and the forms these recurring topics take today.

For this presentation the term biokinetics is interpreted rather narrowly to mean only physiologic processes happening within the body. It is concerned with how lead is distributed within our body rather than the many processes in the environment that bring the lead to the mouth. These biokinetic models are conceptual, numerical descriptions that could explain observations or predict hypothetical situations. So the emphasis in this article is our changing

understanding of how lead is distributed within the body, how long it resides there, and how it is excreted. Less stress is placed on means of exposure or uptake of environmental lead. Proceeding chronologically, for each epoch the measurements of lead in the body will be presented along with mathematical models in an attempt to trace the convergence of observations from two disparate fields—occupational medicine and radiologic health—into some unified models.

## Early Observations

The earliest clinic observations of lead poisoning noted its peculiar time course. The Devonshire colic, documented by Sir George Baker in 1768, serves as an example (1). It was caused by the use of lead in apple cider presses and vats. Sometimes lead metal was added to the cider to prevent spoilage. The abrupt onset of abdominal symptoms was some time after the patient started to drink the tainted cider, longer than simple food poisoning. The palsy came even later. Even in cases of fatal outcome, the symptoms did not appear with the onset of exposure. The notion was that the delay in onset of symptoms was caused by the accumulation of lead in the body until it reached sufficient levels. Similar experience with industrial lead poisoning, for example, noted by Charles

Dickens in 1861 (2), reinforced this notion that illness, should it come, would not come immediately, but only after sufficient time for the lead to accumulate.

Moving forward to the 1930s in Cincinnati, Ohio, Kehoe et al. (3) reported studies of the absorption and excretion of lead in normal adults and in those with lead poisoning. These included dosing human volunteers and measuring their intakes, outputs, and blood lead levels. Kehoe et al. reported that small, natural amounts of lead are present in human tissues. They used a spectrographic method but did not appreciate until later the role of laboratory contamination of samples. They reported mean blood lead levels of nonexposed adults prior to 1938 to be 58 µg/dl, with 75% being between 20 and 70 µg/dl. Later they reduced this value by about one-half. Kehoe et al. (4) stated that lead intake and excretion were in near balance, and with increased exposure and absorption came increased excretion, but the balance was not neutral. There was some accumulation of lead; about 8% of daily intake in normal adults was retained.

Unfortunately, Kehoe's conclusions were based on small differences in lead content among samples, so small errors produced by unappreciated contamination caused difficulties in measuring lead levels. This was especially true in the normal, nonpoisoned subjects, for example, in comparing the differences between diet, feces, and urinary output and relating the net differences to changes in blood lead levels. Of course, in situations of gross lead intake—more than 1 mg/day—these errors became less important. Furthermore, Kehoe did not seem to appreciate, or did any of his generation of researchers, that, even after he made more adequate blank corrections in 1938 and later and obtained what he thought were normal values for blood lead of less than 30, the values he considered normal were actually those of lead-contaminated urban Americans. Natural lead levels were many times lower.

By 1938 some authors concluded that lead levels in blood were a more reliable index of lead absorption than lead excreted in urine according to Traeger and Schmitt (5) in Germany, who relied on colorimetry. Teisinger (6) and Bass (7) using electrochemical methods, reached the same conclusion. Earlier, using emission spectroscopy, Shipley et al. (8) at Johns Hopkins found that blood lead concentrations were useful

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Abbreviations used: <sup>203</sup>Pb, radioisotope of lead; <sup>204</sup>Pb, stable isotope of lead; <sup>210</sup>Pb, radioisotope of lead; <sup>212</sup>Pb, radioisotope of lead; U.S. EPA, U.S. Environmental Protection Agency.

for the diagnosis of lead poisoning. Similarly, Willoughby and Wilkins reported that blood lead concentrations are more stable than those in urine.

Similar studies were carried out in the 1950s by Imamura (10), who tried to duplicate Kehoe's approach in a Japanese setting. Imamura illustrated the presence of lead in the body. He found that lead accumulated in the bodies of control cases and that lead excretion was always less than lead exposure. Among men who were given first 3 mg and then 6 mg lead daily, cumulative lead excretion never accounted for the total dose, and the balance accumulated daily. About 15% of the dose remained in the body. The mean blood lead among controls was 32 µg/dl, and it reached 80 µg/dl for the lead takers. At most only 10 mg of the absorbed lead would remain in the blood, the other 50 mg was thought to be elsewhere in the body, only to leave slowly over a period of many months.

### Application of Radioactive Tracers

Meanwhile, and separately, during the 1940s tremendous advances were being made with the use of radioactive isotopes in physiology and medicine. It was recognized that many physiologic and biochemical processes, hitherto quite unmeasurable, could be quantified with tracers (11). For example, Shemin and Rittenberg (12) determined the biologic half-life of human red blood cells using a radioactive glycine label.

The mathematical analysis of these tracer experiments was also being formalized. Chemical kinetics were applied to compartments or pools of physiologic interest. By measuring the rates of disappearance of radioactive tracers, it was possible to identify pools of distribution of the compound within the body and estimate both the exchange rates among the pools and the pools' turnover time. These equations took the form of coupled differential equations that had solutions in the form of sums of terms with exponential decay factors. Simple one and two-pool models were written so that experimental data could be converted to rates (13).

Stable isotope tracers as well as radioisotopes were under consideration, using Geiger counters and Nier-type mass spectrometers (14). There was little delay before radioactive tracer methodology and concepts of compartmental analysis were applied to lead measurements. However,

the application of stable isotopes would take another quarter-century. By 1954 the metabolism of lead in dogs was being studied with  $^{210}\text{Pb}$  (20-year half-life) (15). Also, radioactive  $^{203}\text{Pb}$  (52-hour half-life) was used to study tissue uptake of lead in rats (16). Generally these studies examined the uptake of the radioactive lead by different organs and how that uptake and release could be modified by citrate, which was used to treat lead poisoning at the time (17). These and other early applications of radioactive lead are reviewed by Wolf and Fischer (18). By 1957 the use and sophistication of these mathematical models had reached the level of complication necessary to explain the simplest issues of lead biokinetics, a three-pool model (19).

The 1960s saw the joint application of radioactive lead techniques and simple compartmental kinetic models to establish the exchange rates and residence times of lead in body pools. Catellino and Aloj (20) determined the elimination constants of  $^{210}\text{Pb}$  from various rat tissues. They killed 10 groups of five rats from 1 to 336 hr after intravenous administration of a 100-µg dose of labeled lead acetate. They identified slow and fast pools, with rapid elimination from the blood and slow elimination from the bones. They recognized that lead was bound reversibly to tissues.

Another early application of radioactive lead was to examine whether human teeth could serve as good indicators of skeletal lead stores. This was of interest because radioactive lead is an  $\alpha$ -emitter and large internal doses were of concern from the viewpoint of radiologic health. Researchers found that the tooth-to-tooth variability of these extracted adult teeth was 25% within the same individual, which was viewed as troublesome. Correlations between teeth and a postmortem iliac crest specimen were significant. The authors concluded that teeth were as adequate as small bone samples in estimating skeletal burdens of  $\alpha$ -emitting bone-seeking elements. Therefore, as early as 1963, teeth were recognized as biomarkers for lead stores (21).

A significant mathematical advance was the recognition that lead and other trace elements occur in environmental samples, including food and water in concentrations that approach a log-normal distribution. The daily amounts of intake and output from the body were then viewed as randomly distributed. The mathematical distribution for the amount of lead stored in the body as a whole was found to be log-normal (22).

Also in the 1960s, Holtzman (23) at the Argonne National Laboratory considered the dynamics of lead within the body.  $^{210}\text{Pb}$  was a potential radiologic concern on its own, but it also was an indicator of other radon daughter products as well. Special attention was given to the uptake of lead by bone and its residence time there because the skeleton was a key target organ in terms of radiologic safety. The long half-life of  $^{210}\text{Pb}$  (21 years) lends itself to the study of the slow process, which may take decades. Holtzman was among the pioneers who applied numeric models of compartmental analysis to predict lead levels over time in different parts of the human body. Among his observations was a bone retention half-life estimate of 17 years, which has held up well as more recent accumulations of estimates have become available. One recent case report involves being able to measure  $^{210}\text{Pb}$  both in the urine and retained, by  $\gamma$ -emissions from the skull, over a 10-year follow up. It has yielded long-term half-lives of  $16 \pm 1$  and  $18 \pm 5$  years (24).

Barltrop and Smith's work with radioactive lead demonstrated the uptake of lead by red blood cells (25). They also recognized the firm but reversible nature of lead's binding. During the late 1960s and the 1970s, a series of experiments with radioactive lead were carried out including those by Hursh (26), who examined the time course of  $^{210}\text{Pb}$  in dogs and presented a model with four exponential terms. He clearly showed blood and urine elimination dynamics. His other studies on men who inhaled  $^{212}\text{Pb}$  (10-hr half-life) yielded invaluable estimates of absorption and clearance, processes that occur within a day or two (27). He also fed men  $^{212}\text{Pb}$  to calculate gut absorption rates (28). Although these were very useful studies, because of the short half-life of  $^{212}\text{Pb}$ , processes longer than a few days cannot be examined; such processes include blood pool turnover, biliary excretion and other sources of endogenous fecal excretion, or hair or nail uptake. Chamberlain (29) later summarized these efforts, using them to estimate the impact of airborne lead.

### Stable Isotope Tracers

At about this time, from 1970 to 1975, I employed stable isotope tracer methods at University of California Los Angeles (30). My teachers George Wetherill and Joel Kopple enabled me to address the question

of how much lead was entering people by respiration compared to ingestion. In Los Angeles in the early 1970s, this was a matter of concern. We fed the volunteers a low-lead diet supplemented with tracer  $^{204}\text{Pb}$ , which is nonradioactive. As such,  $^{204}\text{Pb}$  has distinct advantages over  $^{212}\text{Pb}$ , which has such a short half-life that phenomena taking more than a few days cannot be investigated. Similarly, it is more useful than  $^{210}\text{Pb}$ , which has such a long radioactive half-life (21 years) and a decades-long biologic half-life that to get measurable amounts of disintegration, the lifetime exposure to radiation would be unacceptably high.

We observed the rapid appearance of the tracer in the feces and urine and its gradual accumulation in the blood (31). After some months, the extent of labeling of the blood did not increase but reached a near steady state, reflecting the mixture of the blood daily inputs: from the labeled diet and the unlabeled air but also some amount from the unlabeled skeletal stores. Consequently, a large part of our efforts—and this included modeling—was required to estimate this skeletal output and account for it as we estimated the relative magnitudes of the two external inputs, air and food. A simple linear model of three well-mixed compartments was sufficient for our purpose.

Skeletal lead output was determined by discontinuing the labeled diet and watching the very slow, long-term disappearance of the tracer in the blood and urine, which is tracer that had been stored in the skeleton during the feeding portion of the study. We also had to know the relative amounts of labeled and unlabeled lead in the skeleton; and although modeling was useful, several iliac biopsies provided an additional estimate of the turnover and pool size of the skeletal pool. So, in the process of trying to estimate the size of the daily respired lead intake, we were forced to estimate the impact of the skeletal pool and to devise a simple three-pool model (32).

We had no doubt that an actual body is composed of many more pools, since we saw different tracer uptake rates in different types of samples: feces, blood, bile, pancreatic secretions, saliva, sweat, facial hair, nails, and bone. Each sample type had a different extent of labeling, so each must come from a different pool, since pools are, by definition, well mixed (33). However, we considered three pools to be sufficient for our study. Additional ancillary information was gathered about gut

absorption factors, the blood pool volume of distribution and its turnover, endogenous fecal excretion, and the urinary clearance rates (34).

The gradual rise and slow decline we saw in tracer lead was remarkably similar to the changes seen in blood lead levels in the occupationally exposed population, which was also being well documented in the early 1970s. Both total lead and tracer lead moved with response times of almost a month plus a smaller, longer term component (35).

This similarity encouraged modelers. By 1977 data were available for both the rapid pools and the slower pools, as different radioactive isotopes with very different half-lives had been used. Also, some radioactive lead is the daughter of  $^{214}\text{Bi}$ , and bismuth distributions are different from lead distributions. For this reason Bernard (36) created a more complete model.

This sluggish response of blood to changes in exposure is caused by the long residence time of lead in blood, about a month (37). The longer term accumulation of lead in the skeleton is seen as a future source of blood lead. This release of stored lead is the rate-limiting factor in its clearance of lead from the blood. Even if the kidneys were functioning with youthful efficiency, filtering lead from the blood plasma, the slow release of lead from bone would still be responsible for blood lead being elevated years after the accumulation of exposure was discontinued. This has been noted also in clinical (38) and industrial settings (39), as well as with stable isotope tracers.

## Recent Efforts

During the 1980s more elaborate models of whole body lead metabolism were presented. Kneip et al. (40) presented a somewhat more complex model with six compartments, based on radioactive lead studies of infant and juvenile baboons. This approach had the advantage of allowing for age-specific changes in lead metabolism, as it was thought to be more appropriate to children than a model based on adult men.

One of the key accomplishments of the 1980s supported by the U.S. Environmental Protection Agency (U.S. EPA) was the establishment of the dose-response relationships between time-varying patterns of exposure to lead and biologic precursors of adverse health effects (41). To this end Marcus (42) created a series of models for the long-term, bone-related activity, considering the bone as

several compartments, as well as considering the blood pool as composed of three quicker pools in blood. These biokinetic models are the precursors of the biokinetic uptake models we are considering today. A six-pool model introduced by Bert et al. (43) in 1989, does a better job than the Bernard model of predicating events with a time scale of months by virtue of its inclusion of pools of intermediary half-lives.

The 1980s also saw additional extension in scope of experimental studies of lead metabolism. Heard and Chamberlain (44) performed a series of experiments with  $^{203}\text{Pb}$  (48-hr half-life). After intravenous injections, gamma counting the  $\gamma$ -ray emission from the feet was used to estimate skeletal uptake. Urinary output and blood samples allowed calculations of the fate of dose and clearance rates. Skeletal uptake, whole blood and plasma, and urinary clearance rates of lead were calculated and compared to other alkaline earth elements, calcium and strontium. In a separate series of studies, adults were fed  $^{203}\text{Pb}$  in solution and incorporated into lamb organ meats and vegetables (45). Coincident ingestion of tea, coffee, beer, calcium, and phosphate were also measured. Absorption rates varied from 3 to 19% and up to 50% while subjects were fasting. Other studies sought better understandings of tracer methodology and factors modulating oral inputs. Compared to the earlier studies with  $^{212}\text{Pb}$ , the longer half-life of  $^{203}\text{Pb}$  allowed for the examination of slower processes. Keller and Doherty (46) studied lead kinetics in developing and adult mice using  $^{210}\text{Pb}$ . They observed that a simple, three-compartment model did not adequately account for brain lead levels.

In addition to whole body kinetics, the many details of cellular lead metabolism received closer attention. For example, Pounds and Mittlestaedt (47) examined the cellular metabolism of lead in isolated rat hepatocytes. Fowler et al. (48) used  $^{203}\text{Pb}$  to study lead interactions with the kidney cortex components such as the brush-border membrane. Rosen (49) examined lead and calcium and the osteocyte. Each of these studies is of interest in terms of the storage and release of lead, but each one also tells us much about the kinetics of the several specific targets of lead toxicity, such as the kidney and subcellular sites.

It is too early to write a history of advances in lead biokinetics in the 1990s, but some accomplishments and trends are quite apparent. Models are not getting any

simpler. At the same time that there has been this elaboration with more and more pools, there have also been efforts to reconcile these mathematical models with epidemiologic data. In a recent review, Mushak (50) noted that recent advances in the area of toxicokinetics of lead are explaining the role of past lead exposure in the values obtained from longitudinal lead studies and intervention trials, and in elucidating the impact of approaching menopause on women who grew up in the 1940s to 1970s when environmental lead levels were generally much higher than they are today.

Three recent modeling efforts are especially worth mentioning here. O'Flaherty (51) has published a series of physiologically based models. This model has been calibrated for children, and has the virtue of containing age-dependent terms for bone growth and bone mass as well as age-dependent ingestion rates and dietary changes. This allows testing of blood and bone lead levels to be more labile during early childhood, tracking environmental levels fairly closely. A similar model was developed for adults (52).

Legett has presented an age-specific kinetic model of lead metabolism (53) that was developed within a physiologically based framework designed to address calciumlike bone-seeking elements. Although originally conceived to address environmental alkaline earth radionuclides, which would include lead, it is a credible and versatile method for examining the response of humans to changes in their lead exposure. A rather complete, elaborate, multiple-pool model is offered with generally linear, first-order transport among the pools. The actual parameters used for each of the 39 pathways were derived, as much as possible, from available experimental tracer data from the literature. These parameters are allowed to change with age. Nonlinear plasma-red cell relationships are introduced. The model is generally consistent with data from a variety of experimental and natural conditions.

The most recent example of such a multipool model is a series of integrated environmental uptake biokinetic models generated by the U.S. EPA. An early example is LEAD, version 0.5, produced by the Environmental Criteria (Research Triangle Park, NC 27709) and Assessment Office, designed in 1991 for use on IBM PC-compatible microcomputers running DOS as a stand-alone software program that uses the concentrations of lead in various environmental media (air, water, soil, etc.) to predict the blood lead distributions in

children of various ages. It consists of interconnected pools or body compartments. The intended use is to assess the consequences of alternative lead exposure scenarios in terms of the percentage of the children whose blood lead would exceed any given standard. These models, with their many pools and transfer rates, can be varied to fit existing blood lead data without regard to the extent of lead in these many intermediate pools. Only the blood lead fit is used as an index of goodness of fit, so there are ample degrees of freedom.

An additional topic that has received increasing attention is the interaction between lead and neurons (54). In the search for the impact of lead at each target organ, it seems the study of neurons offers the chance to examine lead's effects at the lowest effect level. There is a fast-growing body of literature in this area and only one recent example will serve as an introduction. The developing brains of tadpoles were exposed to lead in nanomolar concentrations. Lead reduced the area and branch tip number of retinal ganglionic cell axon arborization. Their stunting by lead was reversed by administering dimethyl-L-succinic acid (DMSA) chelator. Clearly, we need to learn more about lead interactions with target tissues in terms of the kinetics of thresholds and reversibility or permanence of lead's toxic effects.

## Conclusion

Biokinetic models that have been constructed usefully describe the general characteristics of lead toxicity, observations of its clinical course, and laboratory findings. The clinical picture of chronic plumbism is marked by latency of onset of symptoms and by frequent remissions. Responding to changes in exposure, blood lead levels rise faster than they fall. Another peculiar feature of lead toxicity is the relatively large amount of lead that can be held innocuously in the skeleton, while much smaller quantities of lead are toxic to neurons. Also, biokinetic models provide a conceptual framework for interpreting this variety of clinical and laboratory findings. Of course, risk assessment of radioactive lead would be impossible with biokinetic models.

Because opportunities for lead exposure can come from a variety of sources, exposure assessment and risk characterization require the use of biokinetic models. This need extends to children, the occupationally exposed, and elderly adults, whether they be exposed to lead via soil, dust, water, food, or air. At this workshop we

heard how these models are being used as a guide to help risk assessors and managers to identify populations at risk, to predict the effectiveness of intervention, to set clean-up standards, and to determine if a house or neighborhood requires remediation. A better understanding of the extent to which a particular biokinetic model should be used for a certain situation is one of this workshop's main purposes, but such questions are beyond the narrow scope of this historical presentation.

A major limitation of current models is the limited data on which they are based. It is striking how many different attempts at modeling used human data from 1970 to 1975 and how very little new data there is, on adults, children, or chimpanzees. A noteworthy study underway in Australia is watching blood lead isotopic composition change during pregnancy in women who immigrated with unusual amounts of lead stored in their bones (55). Another recent study [Smith et al. (56)] compares lead ratios from bone biopsies with those from blood. These studies directly address the issue of mobilizing bone lead stores. But these ongoing efforts aside, I believe that the field has developed as far as it can without more new data on lead kinetics. Such tracer studies on volunteers are safe, and automated mass spectrometers can now run a rack of samples in one day.

Twenty-five years ago, a study reported lead data for five adult males. For biokinetic studies to be more useful, we should have available much more human data. Also, we could consider how chelators modify these lead pathways and pools. Modeling, particularly including the target sites, also has something to contribute to the questions of thresholds or reversibility or permanence of lead's effects.

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